from the composition, cytokine(s) selected from the group consisting of IL-1, IL-2, IL-3, IL-7, IL-8, IL-9, IL-12, TNF-alpha, TNF-beta, TGF-beta, and oncostatin.

25. (Amended) The composition of claim 1, for use as a therapeutic composition, wherein the cytoklines cytokines isolated are selected from the group consisting of IL-1-alpha, IL-1-beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-11, IL-12, IL-13, IL-1 receptor antagonist (IL-1ra), IFN-alpha, IFN-beta, IFN-gamma, oncostatin, TNF-alpha, TNF-beta, soluble TNF receptor (sTNFR), GM-CSF, G-CSF, and M-CSF.

REMARKS

Reconsideration of the rejections set forth in the Office Action dated August 26, 2002 is respectfully requested. The applicant petitions the Commissioner for a 3-month extension of time. A separate petition accompanies this amendment.

I. Amendments

Claim 1 was amended to replace the term overproducing with overexpressing. Support for the amendment may be found in the specification on at least page 4, line 31 through page 5, line 12. Claim 1 was also amended to recite that the cell line includes a gene that expresses a protein effective to inhibit apoptosis. Support for this amendment may be found in at least original claim 12 and in the specification on page 8, lines 9-11.

Claim 10 was amended to depend from claim 1. Claim 25 has been amended to correct a misspelling.

No new matter has been added by these amendments.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned **"Version with Markings to Show Changes Made."**

II. Sequence Identifiers

Correction of the specification to recite the appropriate sequence identifiers at each place where a sequence is discussed will be forwarded under separate cover.

III. Information Disclosure Statement

As requested by the Examiner, copies of the publications referred to in the IDS filed March

1, 2001 accompany this amendment.

IV. Rejection under 35 U.S.C. §102(b)

Claims 1, 25 and 26 were rejected under 35 U.S.C. §102(b) as being anticipated by Lau (WO 97/08324) in view of Der (*PNAS*, Vol. 92, pp. 8841-8845, 1995). This rejection is respectfully traversed in view of the foregoing claim amendments and following remarks.

The law is well established that in order to anticipate a claim, the prior art must disclose "each and every element" of the claimed invention. *SSIH Equipment S.A.v. U.S. Inc. Int'l. Trade Commission*, 218 USPQ 678, 688 (Fed. Cir. 1983). As stated by the Federal Circuit in *In re Bond*, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990), "[f]or a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference." (Emphasis added). See also, *Glaverbel Societe Anonyme v. Northlake Marketing & Supply, Inc.*, 33 USPQ2d 1496 (Fed. Cir. 1995).

Claim 1 has been amended to recite the limitation that the cell line is transformed with an anti-apoptotic gene. Neither Lau nor Der show or suggest transforming a cell line with an anti-apoptotic gene.

Thus, Lau and Der do not teach every element of the claimed invention, and cannot anticipate the present invention. Accordingly, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. §102(b).

Dependent claims 25 and 26 incorporate all the subject matter of claim 1 and add additional subject matter, which makes them *a fortiori* and independently patentable over Lau and Der.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102.

V. Rejection Under 35 U.S.C. §103(a)

Claims 1, 2, 10, 25 and 26 were rejected under 35 U.S.C. §103(a) as being obvious over Kurimoto (U.S. Pat. No. 5,362,490) in view of Shimizu (U.S. Pat No. 4,474,754).

This rejection is respectfully traversed in view of the foregoing claim amendments and following remarks.

A. The Invention

The present invention, as embodied in claim 1, is directed to a composition containing a

mixture of human cytokines produced by (a) culturing a human cell line (i) capable of producing cytokines, and (ii) transformed with a PKR gene and a gene that expresses a protein effective to inhibit apoptosis in the cell line, in a culture medium effective to cause overproduction overexpression of PKR and the anti-apoptotic protein in said mammalian cell line; (b) treating the PKR-overproducing cell line to induce cytokine production; and (c) isolating cytokines produced by said cultured, PKR-overproducing cell line and secreted into culture medium.

Producing the mixture of cytokines in the manner described and claimed provides two important advantages:

(1) human cytokine producing cells are employed that have the ability to produce the desired, complex mixture of cytokines for use therapeutically; and

(2) the mixture is produced at high levels at a stoichiometric ratio that the body recognizes as a natural mixture of cytokines.

B. The Cited Art

Kurimoto *et al.* is directed to overexpressing a novel human interferon gamma. The reference is not concerned with the problem addressed by the present invention, nor does it suggest the applicants' solution. In particular, the reference does not show or suggest producing a cytokine mixture at a high level that is stoichiometrically similar to that produced physiologically, nor does the reference show or suggest producing the mixture from a single cell line that has been selected for its ability to produce the desired combination.

Shimizu teaches the production of human interferon antibodies. The reference is not concerned with the problem addressed by the present invention, nor does the reference suggest the applicants' solution, or the advantages thereof, for the same reasons applied to Kurimoto.

C. Legal Standard of Obviousness

In determining whether an invention is nonobvious, the PTO has the burden of establishing a case of *prima facie* obviousness. A proper analysis under 35 U.S.C. §103 requires consideration of whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process and whether the prior art would have also revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. See MPEP §2142, citing *In re Vaeck,* 20 USPQ2d 1438, Fed. Cir. 1991.

Thus, for a combination of references to render a claimed invention obvious under 35 U.S.C §103, that combination must provide not only a suggestion of the present invention, but also a reasonable expectation of success in reaching that invention. Under these standards, and as discussed below, the Examiner has not made a *prima facie* case of obviousness. In order for the prior art to provided motivation for combining references along the lines of the invention, the prior art must recognize the advantages to be gained by such combination. As noted above, none of the references cited is concerned with the problem of achieving high levels of production of mixtures of cytokines in selected cells at a ratio that the body recognizes as a natural mixture, nor recognizes or even suggests the possibility of addressing the problem successfully by the overexpression of PKR or an anti-apoptotic protein.

In the absence of such a suggestion, and failing to recognize the problem addressed by the present invention, and its solution, the prior art cannot be said to provide a suggestion or motivation for the claimed invention.

Dependent claims 2, 10, 25 and 26 incorporate all the subject matter of claim 1 and add additional subject matter, which makes them *a fortiori* and independently patentable over Kurimoto and Shimizu.

In view of the foregoing, the applicants submit that none of the above references, alone or in combination, renders the pending claims obvious. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103.

VI. Rejection Under 35 U.S.C. §112, second paragraph

Claims 1 and 10 were rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. This rejection is traversed in view of the following amendments.

Claim 1 was amended to replace the term overproducing with overexpressing. Support for the amendment may be found in the specification on at least page 4, line 31 through page 5, line 12.

Claim 10 was amended to depend from claim 1.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

VII. Double-Patenting Rejection

Claims 1, 2, 10, 25 and 26 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 and 15-22 of application serial no. 10105100. This rejection is traversed for the following reason.

In view of the foregoing claim amendment to claim 1, the claims arepatentably distinct from application serial no. 10105100. The applicants submit that the amendments overcome the rejection for obviousness-type double patenting and withdrawal of the rejection is respectfully requested.

IV. Conclusion

In view of the above remarks, the applicants submit that the claims now pending are in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4405.

Respectfully submitted,

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Version with Markings to Show Changes Made

In the Claims:

Claims 1, 10 and 25 have been amended as follows:

1. (Amended) A composition containing a mixture of human cytokines produced by

(a) culturing a human cell line (i) capable of producing cytokines, and (ii) transformed with a PKR gene and a gene that expresses a protein effective to inhibit apoptosis in the cell line, in a culture medium effective to cause ~~overproduction~~ overexpression of PKR and the anti-apoptotic protein in said mammalian cell line;

(b) treating the ~~PKR-overproducing~~ cell line to induce cytokine production; and

(c) isolating cytokines produced by said cultured~~, PKR-overproducing~~ cell line and secreted into culture medium.

10. (Amended) The composition of claim ~~8~~ 1, wherein the isolating step includes removing from the composition, cytokine(s) selected from the group consisting of IL-1, IL-2, IL-3, IL-7, IL-8, IL-9, IL-12, TNF-alpha, TNF-beta, TGF-beta, and oncostatin.

25. (Amended) The composition of claim 1, for use as a therapeutic composition, wherein the ~~cytoklines~~ cytokines isolated are selected from the group consisting of IL-1-alpha, IL-1-beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-11, IL-12, IL-13, IL-1 receptor antagonist (IL-1ra), IFN-alpha, IFN-beta, IFN-gamma, oncostatin, TNF-alpha, TNF-beta, soluble TNF receptor (sTNFR), GM-CSF, G-CSF, and M-CSF.

Attorney Docket: 4099-0002.31 Date: February 26, 2001

Inventor/Applicant: Lau and Wan

Ser./Pat. No. 09/660,468 Filing/Issue Date: September 12, 2000

Paper(s) Enclosed:
Information Disclosure Statement, Form PTO-1449, Cited references.

Fee(s) -none-